

# Transmission of human herpesvirus 8 by sexual activity among adults in Lagos, Nigeria

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**Background:** Human herpesvirus 8 (HHV-8) infection is common in Africa, but prevalence varies geographically. Studies in Europe and America suggest spread through homosexual contact, but evidence of heterosexual spread is inconsistent. We examined the association between HHV-8 and markers of risky sexual activity in Nigeria.

**Methods:** The study subjects included an adult referent population at relatively low risk of HIV infection, patients attending a sexually transmitted disease (STD) clinic, and female commercial sex workers (CSW). Sera were collected between 1991 and 1994 to study the epidemiology of retroviruses and STD in Lagos, Nigeria. Residual samples were tested for HHV-8 antibodies using a K8.1 enzyme immunoassay and for antibodies to syphilis, chancroid, herpes simplex virus 2, HIV-1/2, and HTLV-1. Associations were sought using chi square tests and logistic regression.

**Results:** Overall, HHV-8 prevalence was 26.5% in 2002 study subjects, being higher among CSW and STD patients (31% in each) than in the referent population (19%). HHV-8 prevalence in women was approximately half that in men in both the referent and the STD populations. Increasing age and STD were each associated with HHV-8-seropositivity in men and women, and among women being a CSW was also a risk factor. HHV-8 antibodies were more frequently detected in those with laboratory evidence of STD in each group. Having at least one STD was associated with having HHV-8 antibodies.

**Conclusion:** The higher prevalence of HHV-8 antibody in groups with multiple sexual partners and the association with STD among individuals both support the sexual transmission of HHV-8 in African adults.

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## Introduction

The modes of transmission for human herpesvirus 8 (HHV-8) are not well understood. European and American homosexual men have high antibody prevalence, and seropositivity is associated with the number of reported homosexual partners and sexually transmitted diseases (STD) [1,2]. Recent studies have suggested that spread through heterosexual contact can also occur [2,3], including one performed in South Africa [4]. However, a study of London STD clinic attendees found no evidence of heterosexual transmission of HHV-8 [5]. Importantly, the high prevalence of HHV-8 among children in sub-Saharan Africa [6] and Italy [7], and among Brazilian Amerindians [8] indicates that non-sexual spread to children occurs, whether or not HHV-8 is also spread sexually. In the current study, we tested blood samples from a survey of adults in Lagos, Nigeria, to correlate HHV-8 antibody with sexual activity, as manifest by groups with different sexual behavior, and by laboratory evidence of STD in individuals.

## Methods

Sera from individuals living in Lagos, Nigeria, were collected in 1991, 1992 and 1994 to study the epidemiology of retroviruses (HIV and HTLV) and STD [9,10]. Briefly, interviewers informed subjects about the study and, with their consent, administered a brief questionnaire and obtained blood for serology. Study subjects included healthy individuals at relatively low risk of HIV infection (the referent population) and two higher-risk groups, namely patients attending an STD clinic and commercial sex workers (CSW).

Individuals in the referent population were recruited as convenience samples of healthy individuals from offices and factories and those attending AIDS education seminars ( $n = 475$ ), and from the outpatients' chest clinic ( $n = 67$ ), the family planning clinic ( $n = 25$ ), and a dermatology clinic at the teaching hospital of Lagos ( $n = 199$ ). Collectively, they represent a broad spectrum of the Lagos population, but we do not know how representative they are of the general population. However, we examined data for each subject group separately and found them to be similarly low in their HIV and STD prevalence compared with high-risk groups. We therefore grouped them together for presentation (766 subjects). During 2-month periods in 1992 and in 1994, consecutive attendees with STD or exposed to STD who newly presented at the STD Clinic of the University Hospital of Lagos were invited to participate in the surveys [10]. CSW were approached at brothels or hotels and were invited to

attend general health education workshops or HIV testing sessions at public health offices in Lagos.

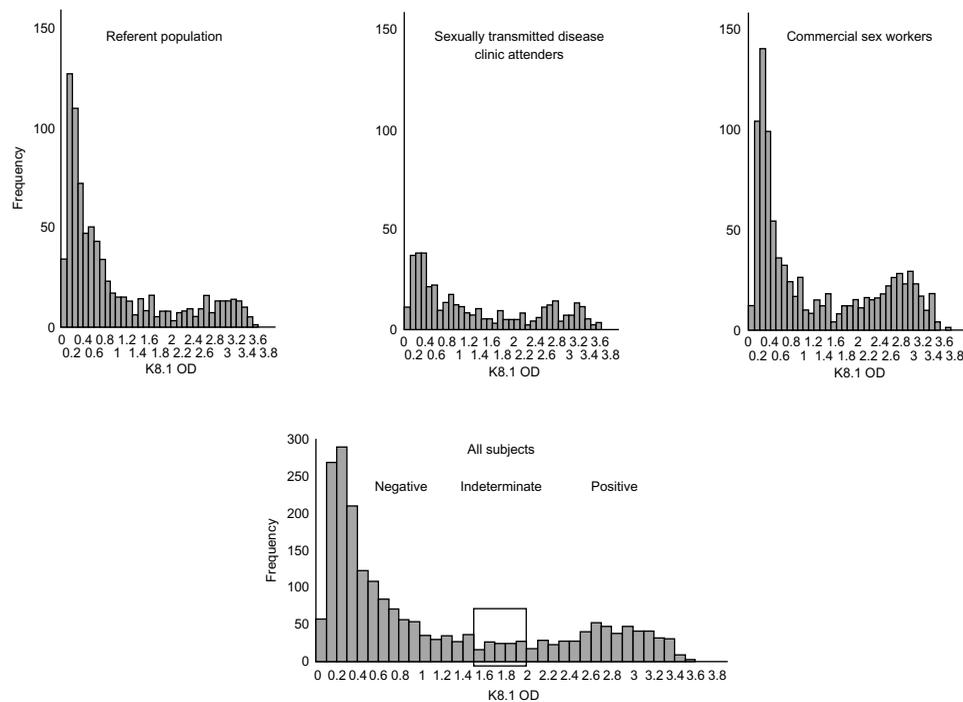
## Laboratory procedures

Samples from 360 subjects (13.3%) in the original studies were depleted by earlier studies. We used an enzyme immunoassay to the K8.1 glycoprotein, a lytic phase antigen, to detect HHV-8 infection. This assay has a sensitivity of 80–90% and a specificity of 95–100% in studies performed on American, European and African populations [11,12]. In these samples, the distribution of the optical density in test subjects had a generally higher background than in tests performed in the non-African populations, but the distribution of results was clearly bimodal (Fig. 1). Therefore, we adjusted the cut-off upward, based on the nadir area of the bimodal distribution, and included an indeterminate zone to reflect our uncertainty about the exact criterion for positivity. Samples with optical densities below 1.5 were considered to be negative, 1.5–2.0 were indeterminate, and above 2.0 were considered to be positive. Subjects with indeterminate results were excluded from the final analysis (5.6% of the referent population, 6.8% of the STD patients, and 5.5% of the CSW).

We also tested the samples on a recently developed enzyme-linked immunoassay against the ORF73 (latent) antigen. Results in this assay closely correlated with results in a standard immunofluorescence assay using latently infected cells (unpublished data). However, because our ORF73 assay has not yet been published, we present analyses using only the results of the already established K8.1 test, except where noted. Commercially available assays were used to detect antibodies against STD as previously described in detail [13]. Antibodies to *Hemophilus ducreyi*, the causative agent of chancroid, were sought by a published but still experimental assay [13]. Positive reactivity is thought to represent both current and past exposure to *H. ducreyi*. We compared HHV-8 prevalence according to demographic and STD variables using the chi-square test and logistic regression analysis. Significance of association was estimated using the likelihood ratio test, and all  $P$  values are two-sided, with  $P < 0.05$  considered statistically significant.

## Results

Samples from 2155 individuals were tested for HHV-8. In analysis, we excluded 123 individuals (5.7%) who had indeterminate results on K8.1 testing, 21 male CSW, and nine subjects who did not have information about sex. The final analysis was performed on 2002 subjects, including 766 subjects in the referent population, 373 STD patients, and 863 CSW. HIV prevalence was higher among CSW and STD patients



**Fig. 1. Histograms of optical density distribution of reactivity to the K8.1 antigen using an enzyme immunoassay for the referent population, for subjects attending the sexually transmitted disease clinic, for commercial sex workers, and for all subjects combined.** The zone considered indeterminate is within the marked box. OD, Optical density.

(15.6 and 11.3%, respectively) than in the referent population (5.0%).

Overall, HHV-8 prevalence was 26.5%, but prevalence varied according to sex and subject category. Table 1 shows HHV-8 prevalence distribution by demographic and sexual variables and by population category among women. Among women, prevalence was highest in CSW (31%), intermediate in STD attendees (20%), and lowest in the referent population (14%), ( $P$  for trend  $< 0.001$ ). Women with chancroid, herpes simplex 2 and HIV were more likely to be HHV-8 seropositive in univariate analysis. Compared with women without laboratory evidence of an STD, those with at least one STD in the referent population were more likely to be HHV-8 positive [unadjusted odds ratio (OR) 2.6; 95% confidence interval (CI) 1.8–3.7]. As expected, the frequencies of laboratory evidence of at least one STD and of each specific type of STD were higher in the STD group than in the referent group and highest among CSW. Among CSW, almost all (93.2%) had laboratory evidence of an STD. HHV-8 prevalence in CSW increased from 27% among those aged 15–24 years to 40% among those aged 45 years or older ( $P$  for trend = 0.012). No individual type of STD was associated with HHV-8 serostatus among CSW. Those CSW with at least one STD had a higher HHV-8 prevalence, but this was not statistically significant (32 versus 22%, respectively,  $P = 0.10$ ). In a model adjust-

ing for age group, having at least one STD and population category among women, CSW were significantly more likely to be HHV-8 seropositive than women in the referent population (OR 2.6; 95% CI 1.6–4.0), whereas positive associations with having an STD or being an STD clinic attender were observed, but these associations were not statistically significant (OR 1.5,  $P = 0.07$ , and 1.3,  $P = 0.36$ , respectively).

Table 2 shows HHV-8 prevalence distribution by demographic and sexual variables and by population category among men. Among men, prevalence was higher in STD attendees than in referent population men (35 versus 22%,  $P < 0.001$ ). Men with syphilis, chancroid, HTLV and HIV were more likely to be HHV-8 seropositive in univariate analysis. Compared with men without laboratory evidence of an STD, those with at least one STD in the referent population were more likely to be HHV-8 positive (unadjusted OR 2.7; 95% CI 1.9–3.9).

Data from these two tables show that referent population and STD attendee men had a higher HHV-8 prevalence than women (22 versus 14%, and 35 versus 20%, respectively;  $P \leq 0.004$ ). Similarly, men had evidence of at least one STD more often than women (50.1 versus 35.2%, respectively, in the referent population, OR 1.5; 95% CI 1.2–1.9). In a model adjusting for age group, laboratory evidence of any STD, and

**Table 1. Human herpesvirus 8 prevalence with sexually transmitted diseases by population category for women.**

Variable	Referent population (N = 287)		STD clients (N = 114)		CSW (N = 863)		OR <sup>a</sup> (95% CI)
	STD prev.	HHV-8	STD prev.	HHV-8	STD prev.	HHV-8	
Overall HHV-8		39/287 (14)		23/114 (20)		271/863 (31)	
Age group (years)							
15–24		14/90 (16)		1/16 (6)		110/410 (27)	Reference
25–34		12/87 (14)		4/46 (9)		125/355 (35)	1.3 (1.0–1.7)
35–44		6/51 (12)		12/31 (39)		27/75 (36)	1.3 (0.8–1.9)
45+		3/33 (9)		4/15 (27)		4/10 (40)	0.7 (0.4–1.5)
		<i>P</i> for trend = 0.32		<i>P</i> for trend = 0.006		<i>P</i> for trend = 0.011	
Syphilis	1.4%		5.4%		3.5%		
Yes		2/3 (67)		1/4 (25)		8/28 (29)	1.2 (0.6–2.4)
No		31/207 (15)		14/70 (20)		251/776 (32)	Reference
		<i>P</i> = 0.015		<i>P</i> = 0.81		<i>P</i> = 0.67	
Chancroid	29.1%		39.7%		88.7%		
Yes		13/59 (22)		7/29 (24)		233/713 (33)	2.0 (1.4–2.8)
No		19/144 (13)		8/44 (18)		25/90 (28)	Reference
		<i>P</i> = 0.11		<i>P</i> = 0.54		<i>P</i> = 0.35	
HSV-2	17.1%		47.2%		60.6%		
Yes		8/49 (16)		9/51 (18)		169/523 (32)	1.4 (1.1–1.9)
No		31/238 (13)		11/57 (19)		102/340 (30)	Reference
		<i>P</i> = 0.54		<i>P</i> = 0.83		<i>P</i> = 0.47	
HTLV-I/II	2.2%		2.8%		3.3%		
Yes		2/6 (33)		0/3 (0)		9/28 (32)	1.2 (0.6–2.4)
No		23/272 (13)		22/106 (21)		254/811 (31)	Reference
		<i>P</i> = 0.16		<i>P</i> = 0.38		<i>P</i> = 0.93	
HIV	4.2%		5.3%		15.6%		
Yes		4/12 (33)		1/6 (17)		46/135 (34)	1.5 (1.0–2.1)
No		35/275 (13)		22/108 (20)		225/728 (31)	Reference
		<i>P</i> = 0.042		<i>P</i> = 0.83		<i>P</i> = 0.47	
Any STD	35.2%		60.5%		93.2%		
Yes		20/101 (20)		14/69 (20)		258/804 (32)	2.6 (1.8–3.7)
No		19/186 (10)		9/45 (20)		13/59 (22)	Reference
		<i>P</i> = 0.024		<i>P</i> = 0.97		<i>P</i> = 0.10	

CI, Confidence interval; CSW, commercial sex workers; HHV-8, human herpesvirus 8; HSV-2, herpes simplex virus 2; OD, odds ratio; prev., prevalence; STD, sexually transmitted disease.

<sup>a</sup>OR for all subject groups.

population group among men, independent predictors of HIV serostatus were having an STD (OR 2.9; 95% CI 2.0–4.1) and being an STD clinic attendee (OR 2.0; 95% CI 1.4–2.8). To estimate the independent effect of sex, we constructed a model adjusting for sex, having an STD, age group, and population category, but excluding CSW. Women were approximately half as likely to be HHV-8 seropositive as men (OR 0.53; 95% CI 0.38–0.74) and associations were still evident with having an STD and being an STD clinic attender (OR 2.4; 95% CI 1.7–3.2, and 1.8; 95% CI 1.3–2.4), respectively).

Several specific types of STD were associated with HHV-8 seropositivity in univariate analysis, but because of its high prevalence, chancroid dominated the association. This chancroid test was experimental, but the significant association between HHV-8 seropositivity and having at least one STD was still evident, but was somewhat attenuated even when we excluded chancroid (OR 1.71; 95% CI 1.20–2.43). The odds ratio for HHV-8 seropositivity was 2.2 (95% CI 1.52–3.18) among the referent population compared with

2.77 (95% CI 1.71–4.52) for the STD group and 1.67 (95% CI 0.89–3.15) for CSW. Overall, the HHV-8 prevalence was 26.5% using K8.1 and 31.5% using ORF73 (kappa 0.77). The demographic and STD associations observed with the K8.1 results were still present when analyses were performed using the ORF73 result only or when using reactivity in either test as positive.

## Discussion

Our study found an increased risk of being HHV-8 seropositive among individuals with markers of risky sexual activity. As this association was seen in both women and men, these results are probably related to heterosexual contact. CSW were more than twice as likely to be HHV-8 seropositive than women in the referent population. Similarly, patients attending an STD clinic also had a higher HHV-8 prevalence than those in the referent population. Within specific population categories, those with laboratory evidence of at

**Table 2. Human herpesvirus 8 prevalence with sexually transmitted diseases by population category for men.**

Variable	Referent population (N = 479)		STD clients (N = 259)		OR <sup>a</sup> (95% CI)
	STD prev.	HHV-8	STD prev.	HHV-8	
Overall HHV-8		107/479 (22)		91/259 (35)	
Age group (years)					
15–24		23/104 (22)		12/40 (30)	Reference
25–34		34/186 (18)		52/137 (38)	1.1 (0.7–1.8)
35–44		20/94 (21)		18/57 (32)	1.0 (0.6–1.8)
45+		22/75 (29)		7/19 (37)	1.4 (0.8–2.4)
		<i>P</i> for trend = 0.32		<i>P</i> for trend = 0.006	
Syphilis	4.0%		5.2%		
Yes		7/14 (50)		6/7 (86)	3.6 (1.5–9.1)
No		82/337 (24)		60/127 (47)	Reference
		<i>P</i> = 0.031		<i>P</i> = 0.05	
Chancroid	57.6%		75.6%		
Yes		57/198 (29)		58/102 (57)	2.2 (1.5–3.4)
No		29/146 (20)		10/33 (30)	Reference
		<i>P</i> = 0.06		<i>P</i> = 0.008	
HSV-2	11.5%		15.2%		
Yes		17/55 (31)		13/38 (34)	1.3 (0.8–2.2)
No		90/424 (21)		76/212 (36)	Reference
		<i>P</i> = 0.11		<i>P</i> = 0.85	
HTLV-I/II	3.5%		6.3%		
Yes		5/16 (31)		9/15 (60)	2.5 (1.2–5.3)
No		97/448 (22)		66/222 (30)	Reference
		<i>P</i> = 0.36		<i>P</i> = 0.015	
HIV	5.4%		13.9%		
Yes		8/26 (31)		15/36 (42)	1.7 (1.0–2.9)
No		99/453 (22)		76/223 (34)	Reference
		<i>P</i> = 0.29		<i>P</i> = 0.38	
Any STD	50.1%		57.3%		
Yes		68/240 (28)		71/6149 (48)	2.7 (1.9–3.9)
No		39/239 (16)		20/110 (18)	Reference
		<i>P</i> = 0.002		<i>P</i> < 0.001	

CI, Confidence interval; CSW, commercial sex workers; HHV-8, human herpesvirus 8; HSV-2, herpes simplex virus 2; OD, odds ratio; prev., prevalence; STD, sexually transmitted disease.

<sup>a</sup>OR for all subject groups.

least one STD were more likely to be HHV-8 seropositive than those without STD. We interpret our findings as suggesting that STD are a marker of sexual promiscuity rather than that STD are a specific co-factor. Taken together, our findings of HHV-8 associations with subject category and with STD suggest that the sexual spread of HHV-8 occurs in this population.

Men were almost twice as likely to be HHV-8 seropositive as women. We also found that having laboratory evidence of an STD was 1.5-fold more common in men than in women in the referent population, which is consistent with men having more promiscuous sexual behavior. Therefore, the higher HHV-8 prevalence in men and in CSW is thus compatible with HHV-8 transmission in adults by sexual routes. However, we cannot exclude the possibility that sexually transmitted diseases act by increasing the likelihood of infection, either because partners with STD are more infectious or because subjects with STD are more susceptible.

Children in Africa, Italy and South America have a high prevalence of HHV-8, which indicates that non-

sexual routes of spread are common, perhaps occurring via saliva exposure [6–8,14]. However, our casual knowledge of African populations does not suggest kissing as a likely mechanism among adults. Kissing as an expression of intimacy is commonly practised in western populations but is not commonly practised by African adults [15]. Furthermore, it is unlikely that kissing would explain the high HHV-8 prevalence in CSW. Our findings of an association of HHV-8 with sexual promiscuity among adults in Lagos might be explained by a small risk of transmission associated with a very common exposure. Such a small risk would be difficult to demonstrate in a homogenous general population but is demonstrable in sexually heterogeneous groups, such as those we studied.

In east and central Africa, HHV-8 prevalence in adults is reported to be 70–90% [12,16–18]. The difference in HHV-8 prevalence between west and east Africa is puzzling. Our findings with K8.1 were confirmed by testing for antibody against another HHV-8 antigen, ORF73. Given the excellent agreement we found using these two assays, our results are probably valid. In this study, because of the high background reactivity in

Nigerians, we chose conservative values and excluded individuals in an indeterminate zone in order to optimize the validity of our comparisons. We may therefore have underestimated HHV-8 prevalence by the 5.7% of individuals excluded as being indeterminate. We performed a sensitivity analysis by categorizing the indeterminate either as HHV-8 seronegative or as seropositive. In each case, the association with having at least one STD remained. The OR was 2.12 (95% CI 1.71–2.63) when indeterminate subjects were coded seropositive, and 2.46 (95% CI 1.94–3.12) when coded as seronegative. We are thus confident that the association between HHV-8 seropositivity and having multiple sexual partners, as measured by being in a group with multiple sexual partners or by having laboratory evidence of STD is valid. These findings, therefore, support sexual transmission as one route of HHV-8 infection in African adults.

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